The Unhealthy Posterior Pituitary

Introduction

The posterior pituitary in the Endocrine module is all about antidiuretic hormone (ADH). We cover oxytocin in the Reproduction module. In this lesson, we explore the function of ADH in detail and call attention to common pitfalls encountered by learners. Specifically, the difference between **volume** (aldosterone) and **concentration** (ADH), and even more specifically, the difference between the physiological sodium of "salt" and the sodium of the basic metabolic profile.

You saw sodium, preload, volume, and aldosterone in Cardiac. Aldosterone and the RAAS were mentioned in Cardiac, explored in Renal, and will be discussed in greater detail in the Adrenal series of this Endocrine module. ADH was discussed in the context of water reabsorption in Renal and is fleshed out here. This has a much more clinical flair than most lessons. It's crucial that you understand the concepts of "volume status" vs. "osmolar status" upfront to avoid later complications in learning. A common error seen in Internal Medicine interns is the failure to recognize the elderly nursing-home patient with dementia as being both volume and water depleted. Colloquially in practice, "dehydrated" means "volume-depleted." But technically, dehydration means normal volume status but free-water deficient. This racks the brains of many trainees. Nipping it in the bud early in your training will save you much brain ache and serve your patients well.

Physiology of the Posterior Pituitary

The posterior pituitary is the reservoir for posterior pituitary hormones. The neurons within the hypothalamus (supraoptic and paraventricular nuclei) are either ADH-making-and-secreting neurons or oxytocin-making-and-secreting neurons. The hormone the neurons will release is constantly being synthesized, packaged, and dispatched to the distal axons. These cells behave like the neurons of a synapse. Discharge of the cell body results in depolarization at the axon terminal, resulting in calcium influx. Calcium influx is the catalyst that induces vesicle fusion with the plasma membrane and exocytosis of peptide hormone into the fenestrated capillaries. **The hormones are made all the time but released in response to depolarization.**

The two hormones the posterior pituitary makes are ADH and oxytocin. ADH and oxytocin are small molecules, only seven amino acids in length. They also differ from one another by only two amino acids. However, they have very different effects. Oxytocin is discussed in the Reproduction module.

Antidiuretic hormone (ADH) is released in response to **low circulating volume** (volume contraction), and also when the plasma is concentrated, when the patient is **hypertonic** (free-water deplete). Dehydration and volume depletion are often used synonymously in clinical practice. In understanding the basic sciences, however, they are very different. When there is not enough free water, the patient is dehydrated and will present with hypernatremia, which indicates hypertonicity. There are no hemodynamic consequences because the volume of plasma is normal, only concentrated. When there is not enough volume, the patient is volume depleted and will present with hemodynamic changes. Volume is preload in the MAP equation, and thus the symptoms will be due to alterations in those parts of the MAP equation.

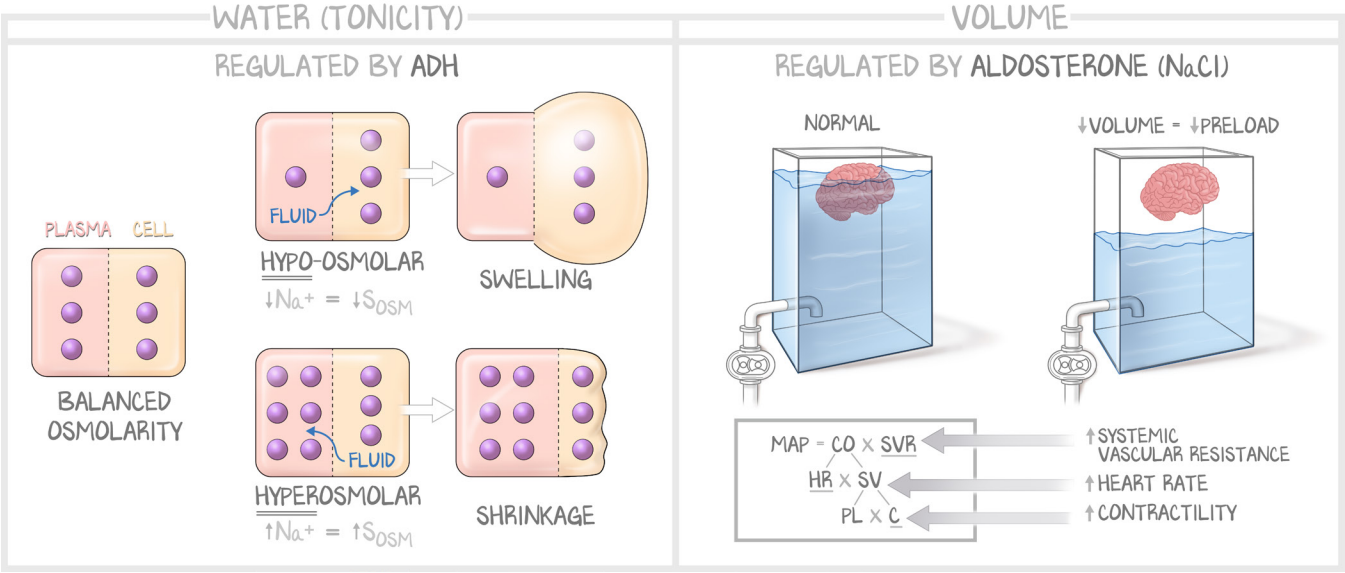

Figure 4.1: Water vs. Volume
Water (tonicity) is about fluid shifting into or out of cells. When volume stays relatively the same, but excess water is added/reabsorbed to that volume, that volume becomes dilute. To balance the plasma, water flows into cells, and thus the cells swell from taking on that water. Conversely, with less water added/reabsorbed, the same volume of plasma becomes concentrated. To balance concentrated plasma, water leaves cells, leading to cell shrinkage. Both shrinkage and swelling are bad. Tonicity impacts individual cells. Volume (sodium) is about perfusing organs. When volume changes but concentration remains relatively the same, there are hemodynamic consequences, and therefore hemodynamic symptoms. Rather than cells swelling or shrinking, the effects of changes in volume are systemic, as taught in Cardiac.

Dehydration, the absence of water, means the plasma is concentrated. The plasma volume may be appropriate—there is no tachycardia or increased contractility to accommodate perfusion pressure deficits due to the lack of preload. The tonicity, however, may be off. When the posterior pituitary detects concentrated plasma, it releases ADH. ADH is responsible for the insertion of aquaporin channels in the collecting duct, reabsorbing water. ADH also stimulates thirst and induces the person to drink water. The inverse is true as well; when the plasma is diluted, ADH secretion stops. This is regulated by a separate set of neurons called **osmoreceptors**, which are intentionally susceptible to alterations in the extracellular matrix. When the extracellular fluid becomes too concentrated, fluid is pulled by osmosis out of the osmoreceptor cell, decreasing its size and **initiating an increased rate of firing**, which induces neuronal discharge and ADH release. Conversely, when the extracellular fluid becomes too diluted, water moves by osmosis in the opposite direction, into the cell, and the increase in cell volume **decreases the** rate of firing and terminates ADH secretion.

Volume depletion is the loss of preload and impacts hemodynamics. Atrial stretch receptors, as well as carotid and aortic bodies, continually assess the blood pressure. When there is excess volume, they are stretched. In regard to ADH, that stretching inhibits signals to the hypothalamus, and there is no stimulus for ADH release. When there is volume depletion, they relax. When relaxed, they disinhibit the hypothalamus and, therefore, **trigger ADH release.** This also disinhibits the medulla and the sympathetic nervous system, resulting in increased cardiac and vessel stimulation (baroreceptor reflex, Cardiac: Hemodynamics #4: *Blood Pressure Regulation*). Volume depletion also compromises the glomerular filtration rate. That results in the activation of the renin-angiotensin-aldosterone axis. Aldosterone induces the insertion of epithelial sodium channels (ENaC channels—Dr. Williams uses his own colloquialism, "eenack channels," when he speaks, even though saying "channels" is redundant) into the collecting duct, enabling more sodium to be reabsorbed. ADH induces the insertion of aquaporins into the collecting duct, enabling the reabsorption of water. This leads to volume expansion without alteration of the tonicity.

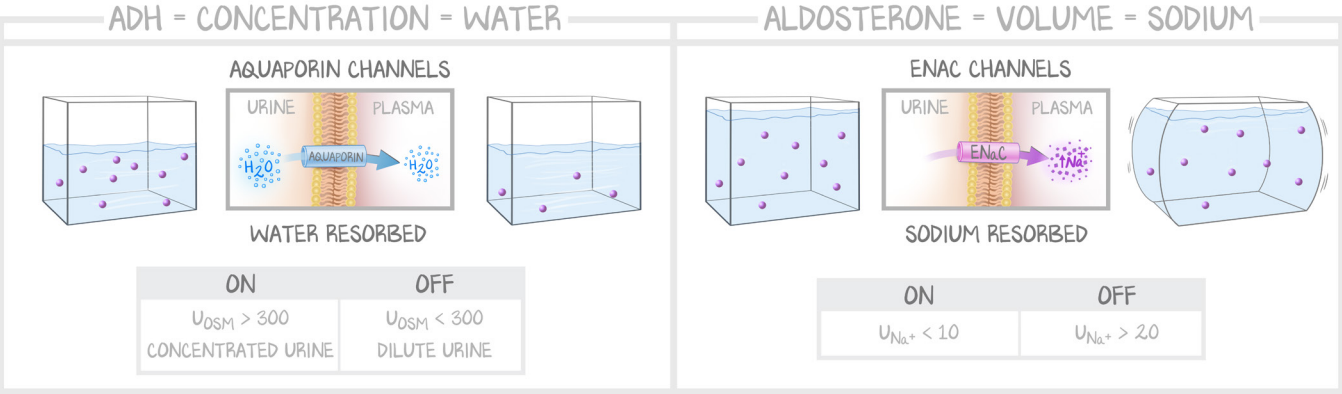

Figure 4.2: Water and Volume as Hormones
Antidiuretic hormone causes the insertion of aquaporin channels in the collecting duct. These channels enable water to be reabsorbed. This amount of water does not affect circulating volume but does change the concentration, the tonicity of plasma. By removing water from the tubules, ADH also removes water from the urine, concentrating it. ADH is "on" when urine osmolarity is high, when U_{osm} > 300. Water, tonicity, ADH, and the sodium on a BMP should all be considered synonymous. Aldosterone is responsible for the insertion of ENaC channels in the collecting duct. These channels enable sodium to be reabsorbed. Reabsorbing sodium causes volume expansion. Because sodium is removed from the tubules, sodium is removed from the urine. Low sodium is an indication that aldosterone is on. The sodium level in the urine determines whether aldosterone is on or off. The sodium level on the BMP is a reflection of tonicity, not of aldosterone activity.

Antidiuretic Hormone

ADH is released appropriately from the posterior pituitary in times of increased tonicity (assessed by osmoreceptors in the hypothalamus) and low circulating volume (assessed by the absence of distention of the right atrium, carotid baroreceptors, and aortic baroreceptors). ADH is released into the bloodstream, where it acts on the collecting duct of the nephron by binding to the ADH receptor. The ADH receptor in the cells of the collecting duct are GPCRs and utilize the G_s-AC-cAMP-PKA second messenger system. This leads to the phosphorylation of specialized vesicles in the cytoplasm. The membranes of these vesicles have the transmembrane protein **aquaporin** in them. The fusion of the vesicle with the luminal plasma membrane results in increased permeability to water. In the absence of ADH receptor stimulation, the reverse process occurs, with dephosphorylation resulting in the involution of the vesicle. These changes happen in a matter of minutes, allowing for very tight regulation of water reabsorption.

Excess ADH causes excess water to be absorbed from the tubules relative to sodium. This results in hypotonic plasma, as evidenced by hyponatremia. Because water is being pulled out of the urine, the urine is concentrated. **Low serum osmolarity** and **elevated urine osmolarity** are indicative of **excess ADH**.

Deficient ADH causes water to be lost in the urine relative to sodium. This results in hypertonic plasma, as evidenced by hypernatremia. Because water is being lost in the urine, the urine is diluted. **Elevated serum osmolarity** and **low urine osmolarity** are indicative of **deficient ADH.**

In truth, as we will see, the symptoms of excess ADH and deficient ADH actually mean excess ADH-receptor activity and deficient ADH-receptor activity. But in keeping things simple to get started, just think ↑ADH and ↓ADH.

Syndrome of Inappropriate ADH (SIADH)

ADH is a posterior pituitary hormone and has no receptor that leads to its activation, so there is no endocrine axis to be dysfunctional. Because terminal axons of neurons release ADH in the posterior pituitary, lesions of either the hypothalamus (where the neuron cell bodies are) or the posterior pituitary (where the axons of those neurons are) would lead to the loss of ADH. Strokes in that region are rare but represent a possible etiology of ADH deficiency. Because ADH is released from neurons and neurons don't proliferate, there isn't a chance to get an overproducing tumor; therefore, excess ADH is rarely a problem with the posterior pituitary. All of this says, "*excess ADH is likely to be external to the posterior pituitary, and deficient ADH can be due to a stroke or mass lesion in the posterior pituitary and is not likely to be a problem with the hypothalamus.*" Indeed, SIADH is a symptom most often of **pulmonary lesions**. Although the lung can make ADH (therefore, any lung pathology could result in SIADH), SIADH is most classically associated specifically with paraneoplastic syndrome due to **small-cell lung cancer**, a neuroendocrine tumor. Because small-cell lung cancer is cancer, there is **no endocrine regulation**. Because small-cell lung cancer is a malignancy that makes ADH, it should be found **outside the pituitary**.

Regardless of how low the plasma osmolarity gets, the cancer will continue to produce ADH. Tonicity, osmolarity, and how concentrated the plasma is can all be estimated using the **serum sodium** level. The lower the sodium, the lower the osmolarity; the higher the sodium, the higher the osmolarity. A direct **serum osmolarity** can also be measured, but serum sodium comes with serum chemistries and is a routine lab test. Low serum sodium does not always equate with a low serum osmolarity, however. Other osmotically active compounds (alcohol, glucose) contribute to serum osmolarity. If they are in excess, then the sodium level may be low, but the osmolarity normal. For every 100 mg/dL above 100 mg/dL of glucose, sodium can be corrected by 1.6. That is, for a reported sodium level of 130 and glucose level of 500 (which is 400 over 100 mg/dL, so 4 100s), the correction is 4 × 1.6 = 6.4; the actual sodium is 136.

The treatment of SIADH starts with removing the underlying cause—treating the cancer, eliminating the traumatic brain injury, or removing the offending agent. When that isn't possible, there are interventions that can be attempted to keep the patient near-normal concentrations. **Water restriction** is one of them. Because the kidneys are reabsorbing more water than they should, and the person cannot simply urinate off the extra water, they can maintain homeostasis by simply drinking less. The addition of **salt tablets** will improve their sodium levels, although that does not get at the heart of the problem. In irreversible conditions where sodium is significantly impaired, medications such as **demeclocycline** (an antibiotic that also blocks ADH-mediated reabsorption of water) or any medication that ends in **-vaptan** (intentionally inducing diabetes insipidus by blocking the ADH receptor) can be used.

Hyponatremia is most commonly caused by medications—thiazide diuretics, antidepressants, and antiepileptic drugs (although on a licensing exam, keep an eye out for that small-cell carcinoma). Isovolemic hyponatremia can also be caused by renal tubular acidosis, Addison's disease, and hypothyroidism, conditions that must be ruled out before diagnosing SIADH. Treatment of severe hyponatremia (very low and causing seizures) necessitates the infusion of hypertonic saline. The use of hypertonic saline in any other condition results in too fast a correction of the sodium level and can result in central pontine myelinolysis. Everything in this paragraph is absolutely relevant to know but is also more of a clinical sciences discussion, so it has been kept brief and unbolded. We want you to focus on the correlation between too much ADH and hyponatremia. In clinicals, you will get a patient with hyponatremia, and it is up to you to work backward to deduce the likely cause and figure out how much fluid to give them to correct the sodium deficit.

Diabetes Insipidus

Whereas SIADH causes hyponatremia and concentrated urine, diabetes insipidus (DI) is characterized by **hypernatremia** and **diluted urine**. There are two main types of DI: central and nephrogenic.

In **central DI**, not enough ADH is secreted from the posterior pituitary. This is often caused by the loss of the neural tissue—stroke, anterior pituitary mass compressing the posterior pituitary, or trauma. In **nephrogenic DI,** there is plenty of ADH secreted from the posterior pituitary, but the ADH receptor is defective and cannot hear the signal. Although there are hereditary defects that cause nephrogenic DI, the much more common cause is medication side effects. **Lithium toxicity** is the most characteristic medication side effect that induces nephrogenic DI, although the medications used to treat SIADH (the -vaptans and demeclocycline), if given in excess, could do it, too. Regardless of the cause, the symptoms are the same. In both cases, aquaporin channels are not inserted into the collecting duct, and free water is wasted in the urine. The patient will complain of **polyuria** (excessive urination) and **polydipsia.** The patient loses water in the urine but can often keep up with those losses with increased intake.

The distinction can be elucidated by a **water deprivation test**. In patients with central DI, who have impaired ADH levels, the administration of ADH will correct the defect. In patients with nephrogenic DI, who have impaired ADH receptors, the administration of ADH will not correct the defect. There is a third condition that presents with high urine volume that is dilute and can be diagnosed by the water deprivation test—psychogenic polydipsia (PP). In patients with PP, excessive water is consumed, so excessive water is lost, but the ADH secretion and ADH receptors are intact. The starting point is "lots of diluted urine." The test begins with water deprivation. If the patient has PP, stopping the water consumption will end the water elimination. In PP, the **urine osmolarity corrects with restriction alone**. If the patient has DI, the urine will not concentrate. After water restriction, **vasopressin** (ADH in medication form) is administered. If the patient has central DI, the addition of the missing hormone will correct the urine osmolarity. In central DI, **the urine osmolarity corrects with ADH administration**. In nephrogenic DI, nothing will correct the urine osmolarity.

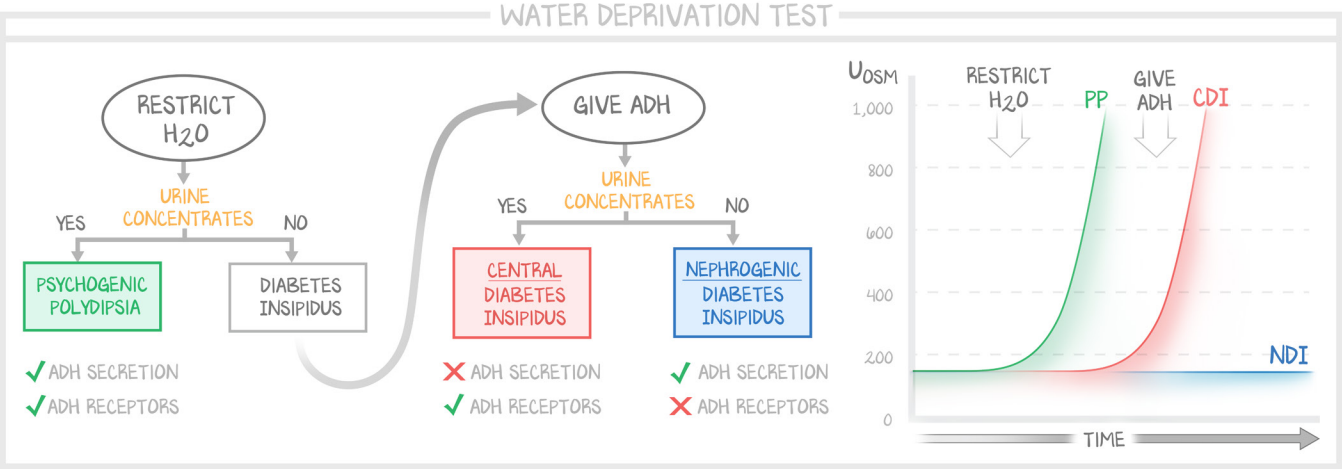

Figure 4.3: Water Deprivation Test
A visual representation of the paragraphs preceding it. PP, psychogenic polydipsia; CDI, central DI; NDI, nephrogenic DI.

Treatment is getting a little past the Basic Sciences. So what we want you to walk away with is this: Don't worry about the treatment for nephrogenic DI; it's too complicated. For PP, stop drinking water. For central DI, give DDAVP (intranasal administration of ADH).